Therapeutic Class Overview
Ophthalmic Antihistamines

Therapeutic Class

- **Overview/Summary:**
  All of the ophthalmic antihistamines listed in Table 1 are Food and Drug Administration (FDA)-approved for the prevention or treatment of the signs and symptoms of allergic conjunctivitis.[1-10] Ketotifen (Alaway®, Zaditor®) is also indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.[6,7] Allergic conjunctivitis is the most common form of ocular allergy. Itching manifests as the primary symptom; however, other common symptoms include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia and tearing.[11] Symptoms usually occur in both eyes, yet one eye may be affected more than the other.[11] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[12] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind histamine receptor sites to reduce itching and vasodilation.[1-10] The ocular antihistamines are relatively selective for the histamine type 1 (H_1-antihistamine) receptor but may also inhibit the degranulation of mast cells, thereby limiting the release of inflammatory mediators such as histamine, eosinophil and neutrophil chemotactic factors.[1-3,5-10] Emedastine (Emadine®) has only H_1-antihistamine activity.[4] Ophthalmic antihistamines have demonstrated a faster onset of action compared to oral antihistamines and ophthalmic mast-cell stabilizers and they are all approved for use in children.[1-11] The most common adverse events associated with these agents are ocular burning, stinging and headache.[1-11] In general, drug interactions are limited due to low systemic bioavailability via the ocular route. The administration schedule for these products ranges from once daily to four times daily, with only alcaftadine (Lastacaft®), olopatadine 0.2% (Pataday®) and olopatadine 0.7% (Pazeo®) are approved for once daily use.[1,9,10] Azelastine (Optivar®), epinastine (Elestat®), ketotifen and olopatadine 0.1% are available generically. Ketotifen is also available over-the-counter.

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alcaftadine (Lastacaft®)	Allergic conjunctivitis†	Ophthalmic solution: 0.25%	-
Azelastine (Optivar®*)	Allergic conjunctivitis†	Ophthalmic solution: 0.05%	✔
Bepotastine (Bepreve®)	Allergic conjunctivitis†	Ophthalmic solution: 1.5%	-
Emedastine (Emadine®)	Allergic conjunctivitis‡	Ophthalmic solution: 0.05%	-
Epinastine (Elestat®*)	Allergic conjunctivitis§	Ophthalmic solution: 0.05%	✔
Ketotifen (Alaway®*, Zaditor®*)	Allergic conjunctivitis§, ocular itching‖	Ophthalmic solution: 0.025%	✔ #
Olopatadine (Pataday®, Patanol®*, Pazeo®)	Allergic conjunctivitis (0.2%)† (0.1%)‡, ocular itching (0.7%)	Ophthalmic solution: 0.1% 0.2% 0.7%	-

* Available generically in one dosage form or strength.
† For the treatment of ocular itching associated with allergic conjunctivitis.
‡ For the treatment of signs and symptoms of allergic conjunctivitis.
§ For the prevention of ocular itching associated with allergic conjunctivitis.
‖ For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.
Product is also available over-the-counter in at least one dosage form or strength.

Evidence-based Medicine

- The ophthalmic antihistamines are significantly more effective compared to placebo for reducing the symptoms of allergic conjunctivitis including ocular itching and conjunctival redness.[15-43]
- Using the conjunctival allergen challenge model for allergic conjunctivitis, ophthalmic bepotastine was shown to be more effective than placebo in relieving ocular itching after 15 minutes and eight hours in adults and children.[18,20]
- Using the conjunctival allergen challenge model, one dose of ophthalmic olopatadine 0.2% was comparable to two doses of ophthalmic olopatadine 0.1%, and both regimens were more effective than placebo in terms of mean itching scores.[22]
- Using the conjunctival allergen challenge model, ophthalmic emedastine and ophthalmic ketotifen significantly reduced the mean itching scores at all time points compared to placebo ($P<0.05$); however, there was no statistically significant difference between ophthalmic emedastine and ophthalmic ketotifen (P values not reported).[24]
- In a randomized controlled trial of patients with seasonal allergic conjunctivitis (N=100), no differences in efficacy were reported between ophthalmic formulations of emedastine, epinastine, ketotifen and olopatadine (P values not reported). All agents were more efficacious in preventing itching and redness compared to ophthalmic fluorometholone ($P<0.001$ for all).[32]\
- Ophthalmic naphazoline/pheniramine was more effective than ophthalmic olopatadine in relieving redness and chemosis, while ophthalmic olopatadine was more effective than ophthalmic naphazoline/pheniramine for relieving itching.[33]
- The safety and efficacy of olopatadine 0.7% (Pazeo®) was based on clinical trials of ophthalmic olopatadine 0.1% (Patanol®) and 0.2% (Pataday®).[8-10]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[13,14]
    - Ophthalmic formulations of agents from the following classes are useful in treating allergic conjunctivitis: corticosteroids, vasoconstrictor/antihistamine combinations, antihistamines, nonsteroidal anti-inflammatories (NSAIDs), mast-cell stabilizers, antihistamine/mast-cell stabilizers and immunosuppressants.[13]
    - An over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist is recommended for mild allergic conjunctivitis. No preference is given to any one OTC antihistamine/vasoconstrictor or antihistamine.[14]
    - If the condition is frequently recurrent or persistent, use mast-cell stabilizers. No single mast-cell stabilizer is preferred over another.[14]
    - Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. No one antihistamine/mast-cell stabilizer is preferred over another.[14]
    - If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used because of the potential for adverse events with their protracted use (e.g., cataract formation and elevated intraocular pressure).[13,14]
- Other Key Facts:
    - Alcaftadine and emedastine are classified as pregnancy category B while the other agents in this class have a pregnancy category C rating.
    - Alcaftadine and olopatadine (0.2%, 0.7%) are the only agents within the class that are approved for once daily use.
    - Ophthalmic formulations of azelastine, epinastine, ketotifen and olopatadine 0.1% are available generically.
    - Ketotifen is also available over-the-counter.

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